REMARKS

I. Claim Status

Claims 1-17, 19-32, 52-57, 59, 73, and 76-92 are pending and currently under examination in the present application. Reconsideration of the pending claims in view of the following arguments and remarks is respectfully requested.

II. Withdrawn Rejections

Applicants acknowledge the Examiner's withdrawal of the previous rejections of claims 1, 5-6, 9-10, 20-22, 55-56, and 59 in view of Valenta et al. (U.S. Patent No. 5,583,046); of claims 1, 5-6, 8-9, 15, 20-24, and 52 in view of Son et al. (1999 Eur. J. Nutr. 38:201-215); of claims 54 and 73 in view of King et al. (2001 J. Immunol. 166(10):6057-6065); and of claims 1-17, 19-32, 52-57, 59, 73, and 76-92 under 35 U.S.C. 112, second paragraph.

III. Rejections Under 35 U.S.C. §112, First Paragraph "Enablement"

Claims 1-17, 19-22, 52-57, 59, 73, and 79-92 have been rejected as allegedly failing to comply with 35 U.S.C. 112, paragraph one, the enablement requirement. More specifically, the Examiner argues that the search to find a suitable scaffold protein with a three-dimensional folding pattern structurally similar to that of the naturally occurring allergen, as recited in the pending claims, would require immense experimentation. (See Office Action at pg. 3). The Examiner has identified several reasons allegedly supporting this argument including that:

(a) the number of allergens is very large, with a large number of potential "scaffold protein" for each one;

(b) the application contains no discussion or explanation for how "structurally similar" the three-dimensional folding pattern of the scaffold protein must be to that of the naturally occurring allergen;

(c) the application contains only a few working examples of actual allergen-scaffold pairs, compared to the very large numbers of

potential "allergens" and "scaffold proteins" encompass by the pending claims; and

(d) the low level of predictability in this field (*i.e.*, a person of ordinary skill would not be able to predict which protein might be structurally similar enough to function as a scaffold). (See Office Action at pg. 4-5).

Regarding point (a), naturally occurring allergens are well known in the art. The skilled artisan in this field would know which proteins are regarded as an allergens in the context of the current invention. A large of number of scientific publications and textbooks are devoted to describing and categorizing allergens including: *Allergy: Principles and Practice*, Middleton et al. Ed., Mosby, 4th Edition, 1993. A copy of Chapter 20, pages 529-540 is provided herewith. Similarly, a copy of Part 3 from: *Essential Allergy*, Mygind et al. Ed., Blackwell Science, 2nd Edition, 1996, is provided as further support for the state of the art relating to known naturally occurring allergens at the time of the priority filing (November 1, 2002). These publications form part of the state of the art of this field and are illustrative of the body of knowledge relating to naturally occurring allergens at the time of the priority filing. As new allergens are identified, they can also be found in numerous publications including an extensive online listing of the International Union of Immunological Societies' at: http://www.allergen.org/List.htm. Copies of these three references are also being submitted concurrently in a Supplemental Information Disclosure Statement.

Furthermore, the specification itself provides a large list of proteins classified as allergens. The specification also provides a general description of allergies and characteristics of allergens in diseases, as well as methods to test for allergenicity (page 3, lines 4-15, page 4 lines 1-16). Finally, the specification provides descriptions for testing allergenicity using e.g. the RAST assay (e.g. page 22).

With regard to point (b), Applicants point out that the application provides explicit guidance enabling a skilled user to practice the claimed invention without undue experimentation. For example, the application contains the following specific structure and folding instructions:

- that the scaffold protein has a level of sequence identity with the naturally occurring allergen of between 30 and 50% [**page 23, lines 5-9**]; and
- that the deconvoluted CD-spectra of the recombinant protein variant deviates less than 30%-compared to the deconvuluted CD-spectra of the naturally occurring allergen [**page 36, lines 13-16**].

With regard to point (c), the application describes a sufficient number of working examples. Scaffold proteins and allergens are explicitly described in the specification (page 38 line 31 to page 39 line 17, page 44 lines 7-13). A lengthy list of suitable allergen – scaffold pairs, including specific allergens from many different allergen sources and their corresponding suitable scaffolds, are provided in the specification at pages 29-36.

It is also taught by the specification that allergen scaffolds are proteins that have a sequence identity with the naturally occurring allergen of below about 67 %, most preferably of between 30 and 50 % (page 23 lines 5-9). The scaffold protein is also taught to have no or little ability to bind to naturally occurring allergen specific antibodies (cross-reactivity), i.e to have reduced antibody affinity binding of preferably a factor of about 10^3 (see page 22, lines 10-22, page 40 lines 6-14 and page 47 lines 7-34).

With regard to point (d), the Examiner argues that the field of protein structure function is unpredictable. However, the state of the art at the time of the priority filing (November 1, 2002) comprised the ability to assess structural similarities based on 3-D structural comparisons or on comparison of modeled structures. The specification describes such a method in Example 4. Additionally, the secondary structure can be assessed in a standard method for comparison of protein folding by Circular Dichroism (CD) analysis. The specification provides that deviation between CD spectra of a naturally occurring allergen and a scaffold protein should be less than 30% and provides further guidance on how to perform and assesses the CD spectra (see page 39 lines 3-9, page 51 lines 13-30, page 53 lines 16-29, page 62 line 26 to page 63 line 28).

Thus, the specification teaches that a limited number of proteins would have the specified sequence identity, reduced antibody cross-reactivity, and desired folding pattern to be suitable scaffold candidates. Skilled artisans would be more than able to practice the present invention without under experimentation in view of the substantial examples and guidance provided in the specification and highlighted herein.

Finally, Applicants point to MPEP 2164.01 (8th Ed., Rev. 4, 2006) that states:

> the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charged Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983).

The field of protein structure/function is a well-developed art and has benefited in the last 20 years from the use of computer programs for predicting 3-D protein structure. In such a mature technology field, a single exemplary species within the scope of the claims substantiates enablement of the claimed genus. In the present case, there are many numerous actual reductions to practice, as well as explicit guidance that serve to enable the claims.

In conclusion, the explicit guidance provided throughout the specification allows the claimed protein variants to be produced without undue experimentation by one skilled in the art. Applicants respectfully request that the rejection of claims 1-17, 19-22, 52-57, 59, 73, and 79-92 under 35 U.S.C. §112, paragraph one, be removed.

IV. Rejections Under 35 U.S.C. §112, First Paragraph "Written Description"

Claims 1-17, 19-22, 52-57, 59, 73 and 79-92 have been rejected as allegedly failing to comply with 35 U.S.C. 112, paragraph one, the written description requirement.

The Examiner states that the skilled artisan cannot necessarily envision all of the proteins with a similar 3-D structure to a selected allergen, or which would be suitable for use as a scaffold protein. The Examiner further reasons that there would be an indeterminate number of allergens from which to select a scaffold protein, since a particular protein may, or may not be classified as an allergen.

The Examiner concedes that the specification contains working examples, but concludes that the specification "fails to disclose all scaffold proteins to all allergens

along with the primary mutations that need to be introduced to the scaffold protein in order to achieve the increased affinity and/or binding capacity to IgE antibodies when compared to the scaffold protein."

Applicants point out that providing working examples for all possible embodiments of an invention is not required. Instead, possession may be shown in a variety of ways including an actual reduction to practice, or any description of relevant, identifying characteristics, so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.[1] Additionally, there are numerous compendiums listing known allergens as described above. Applicants have described many suitable and exemplary allergens. The USPTO guidelines state that the details in the specification need only address that which is new and novel, and not those things that are already known in the art.[2] Thus, it is not necessary for applicants to list every allergen.

As noted above, the specification includes a lengthy list of suitable allergen – scaffold pairs, including specific allergens from many different allergen sources and their corresponding suitable scaffolds (see pages 29-36). Applicants have also already pointed the Examiner to the teachings in the specification relating to predicting the desired secondary structural similarity between the scaffold and allergen. Additionally, Applicants point to the following teachings in the specification:

- suitable mutations (**page 40 lines 16-26, page 42 lines 12-28, page 41 lines 4-7**)
- suitable homologous or identical amino acids for substitution is (**page 15-23, page 59 lines 5-7**) and
- exemplary increased IgE affinity and/or binding capacity (**page 28 lines 10-21, example 5**).

Furthermore, the present invention involves protein structure/function and design, a mature field of technology that has benefited in the last 20 years by the use of computer programs for predicting 3-D protein structure. The specification provides

[1] 66 Fed. Reg., 1099 at 1105, (Jan. 5, 2001).

[2] *Id.* at 1106.

description for the features of the genus characterizing the protein variants encompassed by the present invention. Numerous species are described throughout the specification (see page 29-36) including, *e.g.*, Mal d 1 variant 2760 (modifying an allergen-like epitope to reduce cross-reactivity of the scaffold i.e. secondary substitutions); Mal d 1 variants 2781 and 2762 (modifying an non-allergen like surface on the scaffold to introduce an allergen-like epitope i.e. primary substitution) as examples that have been reduced to practice.

In conclusion, the extensive teachings of the specification and examples reduced to practice provide a more than adequate written description for the full scope of what is claimed. Applicants respectfully request that the rejections of claims 1-17, 19-22, 52-57, 59, 73 and 79-92 under 35 U.S.C. §112, paragraph one, be removed.

V. Rejections Under 35 U.S.C. §102(b)

Claims 1-5, 7-9, 11-14, 19-25, 28, 52-57, 76-78, 90-91 have been rejected as allegedly being anticipated by Holm *et al.*, "Molecular Basis of Allergic Cross-Reactivity Between Group I Major Allergens from Birch and Apple" *J. Chromatography B Biomed. Sci. Appl.* (2001) 756:307-313 ("Holm").

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. *See* MPEP § 2131 (8th Ed., Rev. 4, 2006). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Holm is merely a description and comparison of the deduced amino acid sequence alignments and predicted structural similarity between Bet v1.2801 and various naturally occurring Mal d 1 isoallergens. Holm describes potential antibody binding epitopes in common between these isoallergens, and also points out some potential differences in predicted epitopes (See pg. 312, first column). With regard to the sequence alignment, Holm shows the deduced amino acid sequences of the Bet v1.2801, Mal d 1 (2619) and 15 additional Mal d 1 isoallergens with 57-66% sequence identity that were retrieved from the Swiss Institute of Bioinformatics (SIB). A comparison of these

sequences (Bet v1.2801 and the naturally occurring mal d 1 isoallergens) shows amino acid differences ***between*** the aligned allergens. Holm provides a characterization of these differences as substitutions and shows which ones are considered conservative substitutions, as observed in the sequence alignments. This list is not instructive with regard to ***making a recombinant protein variant by introducing two or more primary mutations spaced by at least one non-mutated amino acid residue according to the present claims***. Additionally, the Holm reference is silent regarding elements of claim 1, including:

- a recombinant protein variant of a scaffold protein;
- the recombinant protein comprises two or more primary mutations spaced by at least one non-mutated amino acid residue, each primary mutation introducing into the scaffold protein at least one amino acid residue identical or homologous to the amino acid residue or residues in the corresponding position in the naturally occurring allergen, and
- the recombinant protein variant has, compared to the scaffold protein, an increased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring allergen.

Since each and every element of the claims is not disclosed in Holm, the rejection of claims 1-5, 7-9, 11-14, 19-25, 28, 52-57, 76-78, 90-91 under 35 U.S.C. 102(a) fails. Applicants respectfully request that this rejection be removed.

VI. Rejections Under 35 U.S.C. §102(e)

Claims 1-17, 19, 53-57, 59, 76-80, 90-92 have been rejected under 35 U.S.C. 102(e) as allegedly being anticipated by King et al. (US patent application 20030039660) ("King '660"). King '660 is similar to King et al. (2001 J. Immunol. 166(10):6057-6065) ("King 2001") that was cited in the previous office action and withdrawn by the Examiner in response to Applicants' arguments of October 17, 2005. Applicants point out that King '660, like King 2001, describes the generation of hybrid insect venom allergens formed by cloning fragments of the *ves v5* gene into the gene *Pol a5*. These insert fragments range in size from 21-150 nucleotides in length and encode amino acid fragments of 7-50 amino acids. Importantly, these insert fragments are all *ves v5* sequence. Thus, King neither teaches nor suggests the protein variants of the present

invention that require the scaffold protein to have "two or more primary mutations spaced by at least one non-mutated amino acid residue."

Since each and every element of the claims 1-17, 19, 53-57, 59, 76-80, 90-92 is not disclosed in King, the rejection of claims under 35 U.S.C. 102(e) fails.

VII. Rejections Under 35 U.S.C. §103(a)

Claims 1, 6, 79-89, and 92 have been rejected under 35 U.S.C. 103(a) as allegedly being obvious in view of Holm.

As discussed in section V *supra*, there is nothing in the Holm reference that would suggest or direct one skilled in the art to make the presently claimed recombinant proteins; it is the present patent application that provides these teachings. Nothing in the Holm reference provides the guidance described above in sections III-V for making the recombinant protein variants and compositions of the present application. Instead, Holm is merely an amino acid sequence comparison between Bet v1.2801, Mal d 1 (2619) and 15 additional Mal d 1 isoallergen sequences obtained from the Swiss Institute of Bioinformatics (SIB).

Applicants respectfully request that the rejection of claims 1, 6, 79-89, and 92 under 35 U.S.C. 103(a) be removed.

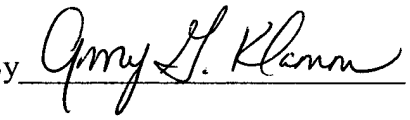
CONCLUSION

Applicants respectfully submit that the amendments and remarks presented here overcome and/or obviate each basis for objection and rejection set forth in the Office Action. The specification and pending claims, as amended, are all believed to be in immediate condition for allowance. Accordingly, the withdrawal of all objections and rejections is respectfully requested. An allowance is earnestly sought.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: April 6, 2006

Respectfully submitted,

By 

Amy G. Klann, Ph.D.
Registration No.: 48,155
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant